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TCF12-Related Bicoronal Craniosynostosis Complicated by a Large Middle Fossa Arachnoid Cyst and Developmental Regression: Case Report and Literature Review

Cindy Li

cindy.li@cuanschutz.edu

University of Colorado Anschutz Medical Campus

John Butterfield

University of Colorado Anschutz Medical Campus

Corbett Wilkinson

Children's Hospital Colorado

Case Report

Keywords: Craniosynostosis, TCF12, Arachnoid Cyst, Autism Spectrum Disorder

Posted Date: March 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8866894/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Child's Nervous System on May 8th, 2026.
See the published version at https://doi.org/10.1007/s00381-026-07309-6.

Abstract

Pathogenic variants in Transcription Factor 12 (TCF12) have been identified as genetic causes of craniosynostosis. The phenotypic spectrum of TCF12-related craniosynostosis is broad and remains incompletely understood. Herein, we report a case of a 2-month old male with a heterozygous pathogenic variant of TCF12 (c.1267C > T; pArg423*) and bicoronal craniosynostosis. He underwent bicoronal suturectomy at 4 months of age, followed by post-operative molding helmet therapy. He returned at 2 years of age with developmental regression including loss of expressive language and fine motor skills. Shortly after he developed clinical findings of elevated intracranial pressure and was found to have synostosis of the sagittal and bilateral lambdoid futures, and a Galassi III left middle fossa arachnoid cyst with significant midline shift, requiring surgical fenestration. Post-operatively, the cyst initially decreased in size with resolution of midline shift. The patient did not regain any developmental milestones and continued to demonstrate deficits in language, social communication, and fine motor function despite resolution of preoperative symptoms of elevated intracranial pressure. To our knowledge, this is the first reported case of TCF12-associated craniosynostosis with a co-occurring arachnoid cyst. Furthermore, there is limited literature describing the long-term neurodevelopmental outcomes of children with TCF12 pathogenic variants. Thus, this case offers expanded insight into the broad phenotypic spectrum of TCF-12 related craniosynostosis and its potential clinical sequelae.

Introduction

Craniosynostosis is a congenital craniofacial disorder that affects approximately 1/2000 newborns and is defined by the premature fusion of one or more cranial sutures[1–3]. Pathogenic variants in Transcription Factor 12 (TCF12) have been identified as genetic causes of craniosynostosis, predominantly in those with premature fusion of the coronal suture(s) [4–7]. TCF12 variants account for approximately 2% of all cases of craniosynostosis[3].

Morphological and developmental outcomes of TCF12-associated craniosynostosis are thought to be relatively mild compared to other causes of syndromic craniosynostosis[8]. However, the long-term sequelae of TCF12-associated craniosynostosis is incompletely understood. There is limited literature describing the development of arachnoid cysts in patients with craniosynostosis, and there have been no reports of TCF12-associated craniosynostosis and co-occurring arachnoid cysts. Herein, we report a case of a 2-year-old male with TCF12-related bicoronal craniosynostosis who underwent bicoronal suturectomy at 4 months of age. He subsequently presented with developmental regression and a rapidly enlarging middle cranial fossa arachnoid cyst requiring surgical fenestration. This case offers expanded insight into the phenotypic spectrum of TCF12-associated craniosynostosis and its potential clinical outcomes.

Case Description

The patient was born full-term by elective cesarean section (39 + 1, 3170g, Apgar scores 8 and 9) after an uncomplicated prenatal course. In the nursery he was noted to have a relatively anteriorly positioned anterior fontanelle but was otherwise healthy. His family history was significant for 15q13.3 microdeletion syndrome and Autism Spectrum Disorder (ASD) in his older sibling. At 2 months of age, he presented with brachycephaly and mild hypotelorism and was found to have bicoronal craniosynostosis (Fig. 1). No arachnoid cyst was definitely seen at this time. He underwent an uncomplicated endoscopic-assisted bicoronal suturectomy at 4 months of age followed by 8 months of helmet therapy, resulting in improvement of his head shape.

The patient underwent genetic testing which revealed a heterozygous pathogenic variant of TCF12 (c.1267C > T; pArg423*). Chromosomal microarray testing was negative including for 15q13.3 microdeletion. Endocrinologic evaluation at 17 months revealed no evidence of anosmia or hypogonadism.

At two years of age, the patient's parents reported concerns for developmental regression including loss of 20–25 words, of signing and pointing behaviors, and of the ability to use eating utensils. He underwent comprehensive developmental testing and was diagnosed with ASD and Global Developmental Delay.

Shortly after, he was found to have bilateral papilledema during a planned ophthalmologic evaluation. CT imaging revealed fusion of the sagittal and bilateral lambdoid sutures, as well as a Galassi Type III left middle fossa arachnoid cyst which was re-demonstrated on MRI (Fig. 2A-C). One month after these findings were identified, he developed symptoms of elevated intracranial pressure (ICP) including headache, fussiness and vomiting.

At 2 years and 6 months, the patient underwent left frontoparietal craniotomy and fenestration of the arachnoid cyst. His post-operative course was uncomplicated, with immediate resolution of headache and vomiting. Post-operative imaging revealed significantly decreased size of the cyst, which remained largely stable for ten months after fenestration without midline shift (Fig. 2D-F). His papilledema resolved. His occipitofrontal circumference (OFC) continued to grow normally with tape measurement, and three-dimensional photogrammetry continued to demonstrate growth in volume. However, the patient did not regain any developmental milestones and continued to demonstrate deficits in language, social communication, and fine motor function.

Discussion

Pathogenic variants in TCF12 are genetic causes of craniosynostosis that have been increasingly reported in the literature [3, 9, 10]. A 2024 review reported 113 published cases of TCF12-associated craniosynostosis to date, with an estimated prevalence of approximately 2% among all patients with craniosynostosis[3]. TCF12 variants occur most frequently in children with coronal craniosynostosis, with estimated frequencies of 32% and 10% of bicoronal and unicoronal cases respectively[4]. However, the condition demonstrates incomplete penetrance and variable expressivity [4, 5, 7, 11].

Overall, long-term outcomes of TCF12-related craniosynostosis appear relatively benign when compared to other syndromic causes[4, 7]. There is a known association between TCF12 variants and isolated GnRH deficiency (Kallmann Syndrome), which manifests with anosmia and hypogonadotropic hypogonadism[12–14] which were not present in our patient. There also appears to be a relatively lower risk of increased ICP and need for revision surgery[3, 7]. Cognitive, behavioral, and psychosocial outcomes are generally normal, with a possible increased risk of social communication deficits[8].

There have been occasional reports of arachnoid cysts in patients with craniosynostosis, primarily in metopic craniosynostosis (trigonocephaly) [15–17]. In one study of 136 patients with trigonocephaly, 39.7% had Sylvian fissure arachnoid cysts, substantially higher than the usual incidence [15]. It is unclear how many of these cases were syndromic, and there have not been any reports of TCF12-related or coronal craniosynostosis and co-occurring arachnoid cysts. Additionally, the risk of developing an arachnoid cyst or of a preexisting cyst growing after craniosynostosis surgery is not well-described.

Our patient developed a rapidly enlarging arachnoid cyst with significant mass effect 20 months after surgery for bicoronal craniosynostosis. The etiology of the cyst remains unclear but it may have been a rare consequence of the TCF12 pathogenic variant, a consequence of surgery, or unrelated to either. Our patient was also found to have early fusion of the sagittal and bilateral lambdoid sutures, which are less commonly involved in cases of TCF12-related craniosynostosis[18, 19]. While multi-suture synostosis can be a cause of increased ICP, our patient experienced immediate and sustained resolution of increased ICP following cyst fenestration, and continued to have normally growing OFC and volume expansion on three-dimensional photogrammetry post-operatively. Therefore, it is more likely that the increased ICP was caused by the cyst itself.

Another unusual feature of this case is our patient's developmental regression. This a finding that has been rarely described in patients with TCF12-associated craniosynostosis. It was apparently unrelated to the arachnoid cyst or elevated ICP, as it did not improve with treatment.

This case highlights the importance of long-term follow-up in patients with syndromic and/or multi-suture craniosynostosis, with a low threshold to obtain imaging in those with atypical findings. Additionally, it reiterates the need for comprehensive developmental assessment in patients with syndromic craniosynostosis, and multidisciplinary collaboration to ensure appropriate management of these sequelae.

Declarations

Author Contributions: CL wrote the first draft of the manuscript and prepared the figures. JB and CW conceptualized the case report, reviewed the manuscript, and provided critical feedback.

Funding: The authors did not receive support from any organization for the submitted work.

Data Availability: All data is presented within the manuscript.

Competing Interests: The authors have no relative financial or non-financial interests to disclose.

Ethics Approval: IRB approval was not required for a single case report.

Consent to Publish: Written informed consent was obtained from the parents.

References

1. Slater BJ, Lenton KA, Kwan MD, Gupta DM, Wan DC, Longaker MT. Cranial sutures: a brief review. Plast Reconstr Surg. 2008;121(4):170e-8e. doi: 10.1097/01.prs.0000304441.99483.97. PubMed PMID: 18349596.
2. Lenton KA, Nacamuli RP, Wan DC, Helms JA, Longaker MT. Cranial Suture Biology. Current Topics in Developmental Biology. 66: Academic Press; 2005. p. 287-328.
3. Foss-Skiftesvik J, Larsen CC, Stoltze UK, Kofod T, Hove H, Bøgeskov L, et al. The role of pathogenic TCF12 variants in children with coronal craniosynostosis-a systematic review with addition of two novel cases. Childs Nerv Syst. 2024;40(11):3655-71. Epub 20240727. doi: 10.1007/s00381-024-06544-z. PubMed PMID: 39060747.
4. Sharma VP, Fenwick AL, Brockop MS, McGowan SJ, Goos JAC, Hoogeboom AJM, et al. Mutations in TCF12, encoding a basic helix-loop-helix partner of TWIST1, are a frequent cause of coronal craniosynostosis. Nature Genetics. 2013;45(3):304-7. doi: 10.1038/ng.2531.
5. Goumenos A, Tsoutsou E, Traeger-Synodinos J, Petychakis D, Gavra M, Kolialexi A, et al. Two novel variants in the TCF12 gene identified in cases with craniosynostosis. Appl Clin Genet. 2019;12:19-25. Epub 20190212. doi: 10.2147/tacg.S190855. PubMed PMID: 30858722; PubMed Central PMCID: PMCPMC6385741.
6. Yilmaz E, Mihci E, Nur B, Alper OM. Coronal craniosynostosis due to TCF12 mutations in patients from Turkey. Am J Med Genet A. 2019;179(11):2241-5. Epub 20190728. doi: 10.1002/ajmg.a.61311. PubMed PMID: 31353793.
7. di Rocco F, Baujat G, Arnaud E, Rénier D, Laplanche J-L, Daire VC, et al. Clinical spectrum and outcomes in families with coronal synostosis and TCF12 mutations. European Journal of Human Genetics. 2014;22(12):1413-6. doi: 10.1038/ejhg.2014.57.
8. Kennedy-Williams P, Care H, Dalton L, Horton J, Kearney A, Rooney N, et al. Neurodevelopmental, Cognitive, and Psychosocial Outcomes for Individuals With Pathogenic Variants in the TCF12 Gene and Associated Craniosynostosis. J Craniofac Surg. 2021;32(Suppl 3):1263-8. doi: 10.1097/scs.0000000000007535. PubMed PMID: 33904513.
9. Choi TM, Kragt L, Goos JAC, Mathijssen IMJ, Wolvius EB, Ongkosuwito EM. Deviating dental arch morphology in mild coronal craniosynostosis syndromes. Clinical Oral Investigations. 2019;23(7):2995-3003. doi: 10.1007/s00784-018-2710-9.
10. Lacroix G, Karnoub M-A, Vinchon M, Wolber A, Martinot V, Guerreschi P. Auricles Anomalies in Patients With a TCF12 Gene Mutation. Journal of Craniofacial Surgery. 2023;34(1).

11. Goos JA, Fenwick AL, Swagemakers SM, McGowan SJ, Knight SJ, Twigg SR, et al. Identification of Intragenic Exon Deletions and Duplication of TCF12 by Whole Genome or Targeted Sequencing as a Cause of TCF12-Related Craniosynostosis. Hum Mutat. 2016;37(8):732-6. Epub 20160602. doi: 10.1002/humu.23010. PubMed PMID: 27158814; PubMed Central PMCID: PMCPMC4949653.
12. Davis EE, Balasubramanian R, Kupchinsky ZA, Keefe DL, Plummer L, Khan K, et al. TCF12 haploinsufficiency causes autosomal dominant Kallmann syndrome and reveals network-level interactions between causal loci. Hum Mol Genet. 2020;29(14):2435-50. doi: 10.1093/hmg/ddaa120. PubMed PMID: 32620954; PubMed Central PMCID: PMCPMC7608740.
13. Celik NB, Sezer A, Genel N, Savas-Erdeve S, Karaman İ, Cetinkaya S. Case report: An adolescent female with anosmic hypogonadotropic hypogonadism, intellectual disability, and papillary thyroid carcinoma: heterozygous deletion of TCF12. Front Endocrinol (Lausanne). 2024;15:1426916. Epub 20240705. doi: 10.3389/fendo.2024.1426916. PubMed PMID: 39036055; PubMed Central PMCID: PMCPMC11257912.
14. Suzuki E, Shima H, Ueda A, Nakabayashi K, Matsubara K, Kuroki Y, et al. De Novo Splice Site Variant of TCF12 in a Boy With Isolated Kallmann Syndrome. Case Reports in Endocrinology. 2025;2025(1):2350842. doi: https://doi.org/10.1155/crie/2350842.
15. Bianchi F, Agostini L, Frassanito P, Massimi L, Tamburrini G. Coexistence of Trigonocephaly and Sylvian Arachnoid Cysts: A Coincidence? Pediatr Neurosurg. 2024;59(2-3):115-20. Epub 20240326. doi: 10.1159/000538559. PubMed PMID: 38531328.
16. Baş NS, Baş S. Postsurgical Size-Changing Temporal Lobe Arachnoid Cysts in Patients with Trigonocephaly Who Underwent Reconstructive Surgery: A Two-Case Report. Pediatr Neurosurg. 2021;56(4):379-84. Epub 20210507. doi: 10.1159/000516207. PubMed PMID: 33965938.
17. Börcek AO, Emmez H, Doğulu F, Baykaner MK. Association of a sylvian arachnoid cyst and trigonocephaly in a developing child: importance and management. Childs Nerv Syst. 2006;22(5):530-2. Epub 20051028. doi: 10.1007/s00381-005-0003-5. PubMed PMID: 16254737.
18. Di Rocco F, Rossi M, Verlut I, Szathmari A, Beuriat PA, Chatron N, et al. Clinical interest of molecular study in cases of isolated midline craniosynostosis. Eur J Hum Genet. 2023;31(6):621-8. Epub 20230203. doi: 10.1038/s41431-023-01295-y. PubMed PMID: 36732661; PubMed Central PMCID: PMCPMC10250395.
19. Paumard-Hernández B, Berges-Soria J, Barroso E, Rivera-Pedroza CI, Pérez-Carrizosa V, Benito-Sanz S, et al. Expanding the mutation spectrum in 182 Spanish probands with craniosynostosis: identification and characterization of novel TCF12 variants. Eur J Hum Genet. 2015;23(7):907-14. Epub 20141001. doi: 10.1038/ejhg.2014.205. PubMed PMID: 25271085; PubMed Central PMCID: PMCPMC4463497.

Figures

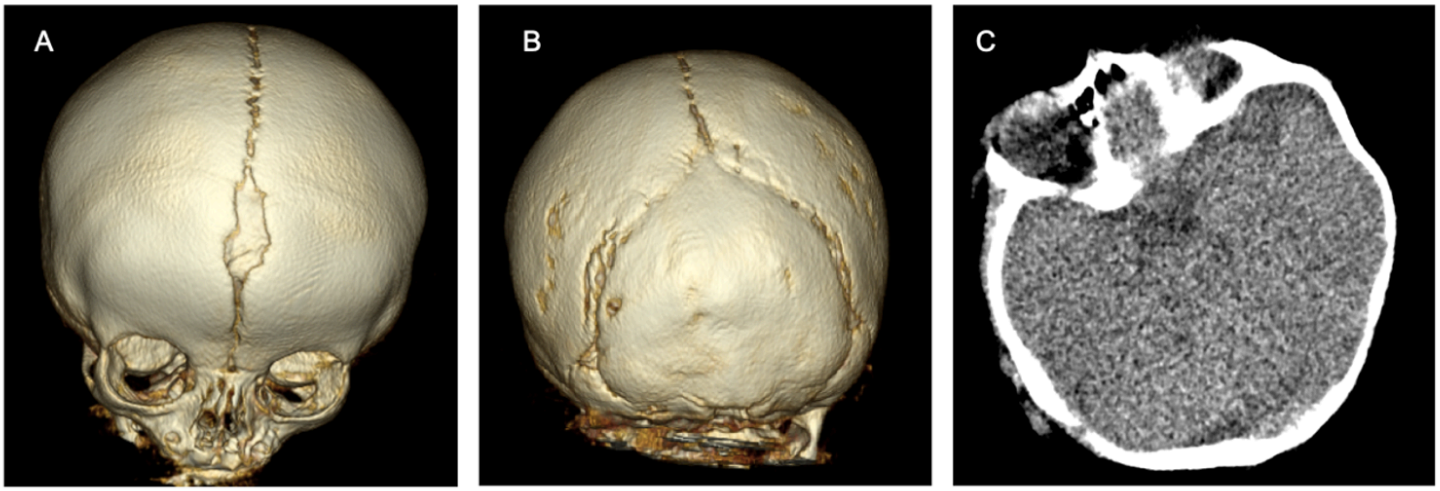


Figure 1

CT findings prior to surgical correction of bicoronal craniosynostosis. A) Three-dimensional reconstruction of CT at 2 months of age demonstrated fusion of the bilateral coronal sutures and B) patent sagittal and metopic sutures. C) Despite limited parenchymal resolution, axial CT at this time demonstrated no definite evidence of an arachnoid cyst.

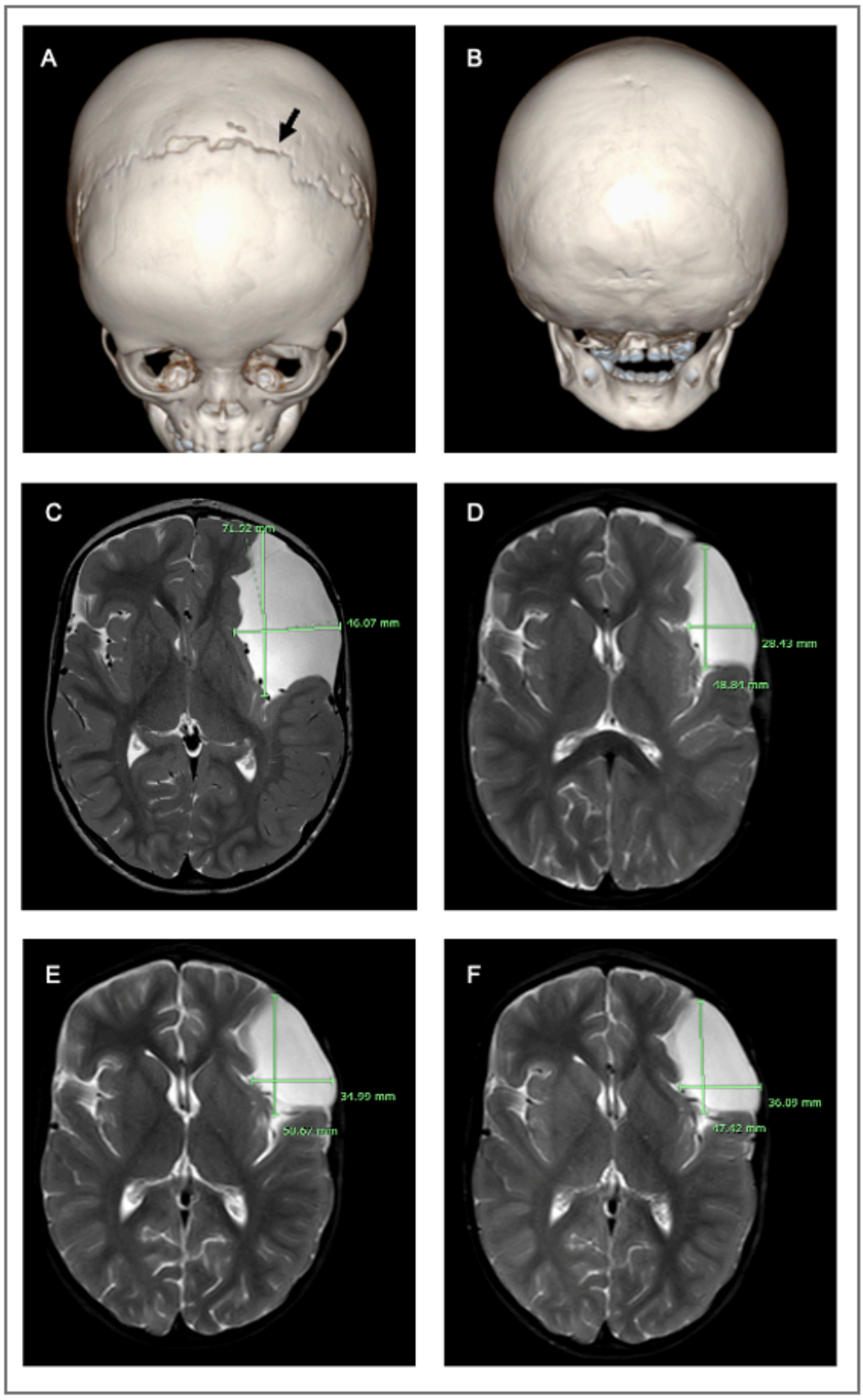


Figure 2

Pre- and post-operative imaging of multi-suture synostosis and the arachnoid cyst. A&B) Three-dimensional reconstruction of CT at 2 years and 5 months of age demonstrated fusion of the sagittal and bilateral lambdoid sutures. The apparent coronal sutures (denoted by the arrow) are at the site of the previous bicoronal craniectomy. C) T2-weighted MR image at this time demonstrated a large left middle cranial fossa arachnoid cyst extending to the left sylvian fissure and lateral to the frontal lobe, with

3.6mm rightward midline shift. D) At 1.5 months after fenestration, the arachnoid cyst decreased in size with resolution of midline shift. E) At 5 months after fenestration, the arachnoid cyst demonstrated slight interval regrowth without recurrence of clinically significant mass effect. F) At 10 months after fenestration, the arachnoid cyst remained stable in size.